Effect of a strategy of comprehensive vasodilation vs usual care on mortality and heart failure rehospitalization among patients With acute heart failure: the GALACTIC randomized clinical trial

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Abstract: Importance: Short-term infusions of single vasodilators, usually given in a fixed dose, have not improved outcomes in patients with acute heart failure (AHF). Objective: To evaluate the effect of a strategy that emphasized early intensive and sustained vasodilation using individualized up-titrated doses of established vasodilators in patients with AHF. Design, Setting, and Participants: Randomized, open-label blinded-end-point trial enrolling 788 patients hospitalized for AHF with dyspnea, increased plasma concentrations of natriuretic peptides, systolic blood pressure of at least 100 mm Hg, and plan for treatment in a general ward in 10 tertiary and secondary hospitals in Switzerland, Bulgaria, Germany, Brazil, and Spain. Enrollment began in December 2007 and follow-up was completed in February 2019. Interventions: Patients were randomized 1:1 to a strategy of early intensive and sustained vasodilation throughout the hospitalization (n = 386) or usual care (n = 402). Early intensive and sustained vasodilation was a comprehensive pragmatic approach of maximal and sustained vasodilation combining individualized doses of sublingual and transdermal nitrates, low-dose oral hydralazine for 48 hours, and rapid up-titration of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or sacubitril-valsartan. Main Outcomes and Measures: The primary end point was a composite of all-cause mortality or rehospitalization for AHF at 180 days. Results: Among 788 patients randomized, 781 (99.1%; median age, 78 years; 36.9% women) completed the trial and were eligible for primary end point analysis. Follow-up at 180 days was completed for 779 patients (99.7%). The primary end point, a composite of all-cause mortality or rehospitalization for AHF at 180 days, occurred in 117 patients (30.6%) in the intervention group (including 55 deaths [14.4%]) and in 111 patients (27.8%) in the usual care group (including 61 deaths [15.3%]) (absolute difference for the primary end point, 2.8% [95% CI, -3.7% to 9.3%]; adjusted hazard ratio, 1.07 [95% CI, 0.83-1.39]; P = .59). The most common clinically significant adverse events with early intensive and sustained vasodilation vs usual care were hypokalemia (23% vs 25%), worsening renal function (21% vs 20%), headache (26% vs 10%), dizziness (15% vs 10%), and hypotension (8% vs 2%). Conclusions and Relevance: Among patients with AHF, a strategy of early intensive and sustained vasodilation, compared with usual care, did not significantly improve a composite outcome of all-cause mortality and AHF rehospitalization at 180 days. Trial Registration: ClinicalTrials.gov Identifier: NCT00512759.

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Effect of a Strategy of Comprehensive Vasodilation vs Usual Care on Mortality and Heart Failure Rehospitalization Among Patients With Acute Heart Failure

The GALACTIC Randomized Clinical Trial

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IMPORTANCE Short-term infusions of single vasodilators, usually given in a fixed dose, have not improved outcomes in patients with acute heart failure (AHF).

OBJECTIVE To evaluate the effect of a strategy that emphasized early intensive and sustained vasodilation using individualized up-titrated doses of established vasodilators in patients with AHF.

DESIGN, SETTING, AND PARTICIPANTS Randomized, open-label blinded-end-point trial enrolling 788 patients hospitalized for AHF with dyspnea, increased plasma concentrations of natriuretic peptides, systolic blood pressure of at least 100 mm Hg, and plan for treatment in a general ward in 10 tertiary and secondary hospitals in Switzerland, Bulgaria, Germany, Brazil, and Spain. Enrollment began in December 2007 and follow-up was completed in February 2019.

INTERVENTIONS Patients were randomized 1:1 to a strategy of early intensive and sustained vasodilation throughout the hospitalization (n = 386) or usual care (n = 402). Early intensive and sustained vasodilation was a comprehensive pragmatic approach of maximal and sustained vasodilation combining individualized doses of sublingual and transdermal nitrates, low-dose oral hydralazine for 48 hours, and rapid up-titration of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or sacubitril-valsartan.

MAIN OUTCOMES AND MEASURES The primary end point was a composite of all-cause mortality or rehospitalization for AHF at 180 days.

RESULTS Among 788 patients randomized, 781 (99.1%; median age, 78 years; 36.9% women) completed the trial and were eligible for primary end point analysis. Follow-up at 180 days was completed for 779 patients (99.7%). The primary end point, a composite of all-cause mortality or rehospitalization for AHF at 180 days, occurred in 117 patients (30.6%) in the intervention group (including 55 deaths [14.4%]) and in 111 patients (27.8%) in the usual care group (including 61 deaths [15.3%]) (absolute difference for the primary end point, 2.8% [95% CI, −3.7% to 9.3%]; adjusted hazard ratio, 1.07 [95% CI, 0.83-1.39]; *P* = .59). The most common clinically significant adverse events with early intensive and sustained vasodilation vs usual care were hypokalemia (23% vs 25%), worsening renal function (21% vs 20%), headache (26% vs 10%), dizziness (15% vs 10%), and hypotension (8% vs 2%).

CONCLUSIONS AND RELEVANCE Among patients with AHF, a strategy of early intensive and sustained vasodilation, compared with usual care, did not significantly improve a composite outcome of all-cause mortality and AHF rehospitalization at 180 days.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT00512759

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Acute heart failure (AHF) is the most common diagnosis in the emergency department leading to hospitalization.[1,2] In contrast to the relevant achievements in management of patients with chronic HF with reduced left ventricular ejection fraction (LVEF), morbidity and mortality remain unacceptably high in patients with AHF.[1]

Early initiation of high-dose intravenous nitrates targeted to arterial blood pressure vs high-dose furosemide and noninvasive positive pressure ventilation improved outcomes in severe pulmonary edema, an AHF phenotype representing about 5% of all AHF cases.[3,4] It is unknown, however, whether early and aggressive vasodilation also provides benefits in the broader AHF population. Short-term infusions of single vasodilators, usually given in a fixed dose, did not improve outcomes in several recent trials.[5-7] Based on favorable safety data on the application of high-dose nitrates as transdermal patches in patients treated in medical wards,[8] the complementary hemodynamic profile of nitrates and hydralazine,[9-11] and the more pronounced benefits observed in patients with chronic HF treated with high vs low doses of angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs),[12,13] it was hypothesized that a comprehensive pragmatic approach of early intensive and sustained vasodilation may improve long-term outcomes in patients with AHF.

Key Points

Question Does a comprehensive approach of early intensive and sustained vasodilation, using a combination of nitrates, hydralazine, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and sacubitril-valsartan, improve outcomes in patients with acute heart failure?

Findings In this randomized clinical trial that included 788 patients hospitalized for acute heart failure, a strategy that emphasized early intensive and sustained vasodilation, compared with usual care, resulted in no significant difference in the primary end point of 180-day all-cause mortality and acute heart failure rehospitalizations (30.6% vs 27.8%, respectively).

Meaning Among patients with acute heart failure, a strategy of comprehensive vasodilation, compared with usual care, did not significantly improve a composite outcome of all-cause mortality and acute heart failure rehospitalizations at 180 days.

Methods

Study Design and Population

GALACTIC was an investigator-initiated, randomized, open-label, blinded-end-point, multinational, multicenter study. The open-label design was selected for 2 reasons: first, to avoid undertreatment in the placebo group of a blinded trial because of concerns of treating physicians regarding the possible risk of applying a second active drug and its associated increased risk of adverse events, including hypotension, in an acute condition with an effective alternative therapy (loop diuretics) to improve congestion[5-7]; second, to allow evaluation of a strategy of rapid up-titration of the ACE inhibitor already in place rather than that of a specific ACE inhibitor. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees and the respective national authorities.[14] All patients provided written informed consent. The trial protocol and the statistical analysis plan are available in Supplement 1. Data management and randomization was overseen by the independent clinical trial unit of the University Hospital Basel, Basel, Switzerland (P.S.).[15]

Patients aged 18 years or older hospitalized for AHF were eligible regardless of their LVEF. The diagnosis of AHF was based on integrated clinical judgment according to clinical guidelines for each period[2] and required New York Heart Association class III or IV dyspnea and elevated B-type natriuretic peptide (BNP) plasma concentrations of at least 500 ng/L or N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations of at least 2000 ng/L. After the approval of sacubitril-valsartan, the protocol was amended to specify that in patients already treated with sacubitril-valsartan, only NT-proBNP, not BNP, could be used for the inclusion of patients and for defining the up-titration scheme for sacubitril-valsartan.[16,17]

Patients who required immediate intensive care unit admission or urgent coronary intervention or who had a systolic blood pressure lower than 100 mm Hg or severe renal dysfunction (creatinine >250 µmol/L [>2.8 mg/dL]) were excluded (a complete list of eligibility criteria is available in eTable 1 in Supplement 2).

The final diagnosis of AHF was adjudicated by an independent cardiologist who had access to all patients' medical records. In situations of uncertainty about the diagnosis, cases were reviewed and adjudicated in conjunction with a second cardiologist (eAppendix in Supplement 2).

Randomization and Study Procedures

For central randomization in a 1:1 ratio to a strategy emphasizing early intensive and sustained vasodilation or usual care according to current guidelines,[2] stratification according to site and BNP or NT-proBNP concentrations was performed using static stratified block randomization schema with secuTrial dedicated data management software (interActive Systems GmbH) (eAppendix in Supplement 2).[18] Early intensive and sustained vasodilation involved a comprehensive pragmatic approach of maximal and sustained vasodilation combining high and individualized doses of sublingual and transdermal nitrates, oral hydralazine for 48 hours to avoid nitrate tolerance and to complement the vasodilating effect of nitrates on veins and large arteries with that of hydralazine on small arteries,[9-11] and rapid up-titration of ACE inhibitors, ARBs, or sacubitril-valsartan according to pretreatment and/or preference of treating physicians, using a predefined safety corridor for systolic blood pressure of 90 to 110 mm Hg (**Box**). To avoid further increases in protocol complexity and the associated risk of reduced protocol adherence, no additional diastolic blood pressure targets were used.

Treatment was initiated with sublingual nitrates or nitrospray (0.8 mg glyceryl trinitrate at randomization and after 10 and 20 minutes), followed by high and maximally tolerated blood pressure–adjusted doses of transdermal nitrates (glyceryl

Box. Strategy of Comprehensive Intensive and Sustained Vasodilation

Day 1 (Treatment Initiation)

Sublingual (or as spray) glyceryl trinitrate, 0.8 mg every 10 minutes for 30 minutes

Transdermal glyceryl trinitrate according to SBP (40-60 mg every 24 hours if SBP ≤130 mm Hg; 60-80 mg every 24 hours if SBP >130 mm Hg)

Oral hydralazine, 25 mg every 6 hours

After 6 hours, up-titration of transdermal glyceryl trinitrate according to SBP (+20-40 mg every 24 hours if SBP is 111-130 mm Hg; +20-60 mg every 24 hours if SBP >130 mm Hg)

Day 2

Up-titration of transdermal glyceryl trinitrate according to SBP (+20-40 mg every 24 hours if SBP is 90-110 mm Hg; +20-60 mg every 24 hours if SBP is 111-130 mm Hg; +40-80 mg every 24 hours if SBP >130 mm Hg)

Oral hydralazine, 25 mg every 6 hours

Initiation of ACE inhibitor, ARB, or ARN inhibitor therapy (eg, ramipril, 1.25 mg/d, if SBP is 90-130 mm Hg; ramipril, 2.5 mg/d if SBP >130 mm Hg); in case of preexisting ACE inhibitor, ARB, or ARN inhibitor therapy, up-titration of dose according to therapy schedule starting on day 2

Day 3

Gradual reduction of transdermal glyceryl trinitrate dose according to SBP on day 3 (50% of day 2 if SBP is 90-130 mm Hg; 75% of day 2 if SBP is 131-150 mm Hg; 100% of day 2 if SBP >150 mm Hg) until hospital discharge; intermittent dosing (12 hours with nitrates, 12 hours nitrate free) from day 3 onward

Up-titration of ACE inhibitor, ARB, or ARN inhibitor therapy according to SBP (eg, ramipril, 2.5-3.75 mg/d, if SBP is 90-130 mm Hg; ramipril, 2.5-5 mg/d if SBP >130 mm Hg)

Days 4 Through 7

Up-titration of ACE inhibitor, ARB, or ARN inhibitor therapy dependent on SBP until reaching the maximum daily recommended dose (eg, ramipril, 10 mg/d).[2]

ACE indicates angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; ARN, angiotensin receptor–neprilysin; SBP, systolic blood pressure. The target SBP of 90-110 mm Hg for the entire hospitalization was considered to represent the maximal feasible afterload reduction without impairment of critical organ perfusion. The protocol included predefined deescalation schema for hypotension, worsening renal function, and uncontrolled hypertension (Supplement 1 and eTable 2 in Supplement 2).

trinitrate) and rapid up-titration of ACE inhibitors, ARBs, or sacubitril-valsartan (eFigure 1 in Supplement 2).[2,12] On day 3, the transdermal nitrate dose was gradually decreased, while up-titration of ACE inhibitors, ARBs, or sacubitril-valsartan was continued until hospital discharge using the target doses recommended in current clinical practice guidelines for chronic HF with reduced LVEF.[1,2] The transdermal application was chosen because it maximizes patient safety in a general medical ward setting; for instance, in the case of arterial hypotension, the most relevant adverse effect of nitrates, the nitrate patch can easily be removed, with usually swift recovery of blood pressure.[8] Individualized doses of nitrates were used, as the dose required to lower intracardiac filling pressures to a relevant extent varies substantially by individual patient.[19,20] In the usual care group, nitrates were restricted to standard low doses, and the suggested up-titration of ACE inhibitors, ARBs, or sacubitril-valsartan during hospitalization was slow. Postdischarge treatment was left to the discretion of treating physicians.[1,2]

Therapies for AHF other than vasodilators, including diuretics, were not affected by the protocol and were provided according to guidelines and the discretion of treating physicians in both groups.[1,2] The protocol defined vasodilator treatment in the intervention group until hospital discharge or day 7, whichever came first. Up-titration of ACE inhibitors (or ARBs or sacubitril-valsartan) until hospital discharge was faster than in the usual care group, so patients in the intervention group were expected to receive a significantly higher dose of ACE inhibitors, ARBs, or sacubitril-valsartan at the time of discharge. It was expected that in clinical practice the difference between groups in the discharge dose of ACE inhibitors, ARBs, or sacubitril-valsartan would persist through most of the 180-day follow-up period.[12] The combination of more rapid lowering of intracardiac filling pressures by high-dose nitrates combined with hydralazine[3,4,21] and higher doses of disease-modifying drugs proven beneficial in HF with reduced LVEF throughout the study period[12,13] was expected to result in improved outcomes. The trial protocol included predefined deescalation schema in case of hypotension or relevant worsening of renal function and suggested treatments for hypertension (Supplement 1 and eTable 2 in Supplement 2).

Outcomes

The primary end point was a composite of all-cause mortality or rehospitalization for AHF at 180 days. An independent clinical events committee, blinded to group assignment, centrally adjudicated all deaths and hospitalizations through day 180.

Secondary end points included but were not limited to the individual components of the primary end point, a composite of all-cause mortality or rehospitalization due to all causes; time to discharge; blood pressure at days 1 through 7; quantitative assessment of dyspnea at levels of 60° and 20° on day 2 and at discharge or on day 6, whichever came first, using a 5-point Likert scale ranging from “none” to “very severe” dyspnea; and NT-proBNP and creatinine concentrations at 48 hours (day 3) and at discharge. A full list of prespecified secondary end points is provided in eTable 3 in Supplement 2.[22] Not all secondary end points are reported herein.

Post hoc analyses were conducted to characterize the implementation of the early intensive and sustained vasodilation strategy and doses of vasodilators, furosemide, and other HF drugs during the course of hospitalization and at 180-day follow-up, and to compare weight reduction during hospitalization. Patients and family physicians were contacted after 90 days and 180 days by telephone or in written form by trained researchers. Further information was obtained by institutional chart review and national registries on mortality.

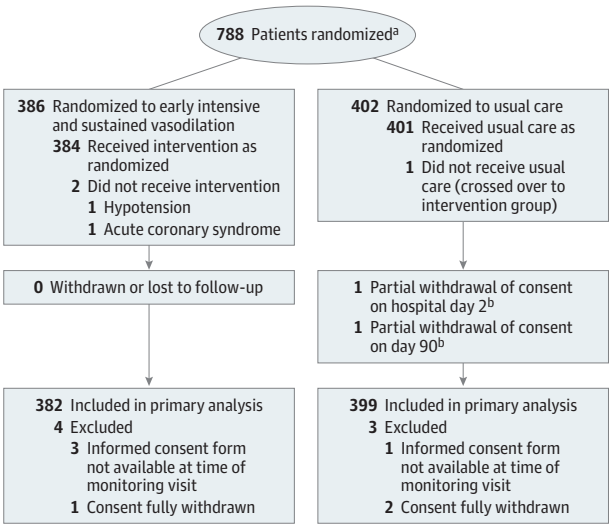
Statistical Methods

Sample size was calculated for superiority hypothesis testing based on outcomes observed in a prior AHF study.[23] A hypothesized 20% reduction of the composite end point of death or AHF rehospitalization within 180 days and an event rate of 48% in the

usual care group was expected to require 385 patients per treatment group to obtain, with a probability of 80%, a log-rank test result that was statistically significant at the .05 level.[3,12] To compensate for an expected 1% to 2% of patients in whom the primary end point could not be assessed at 180 days because of loss to follow-up or complete withdrawal of informed consent, enrollment of 785 patients was planned. No interim analyses were performed. No imputation was performed for missing values. Patients without complete 180-day clinical follow-up were censored at the time of last known contact.

Patients were analyzed according to their randomization group with inclusion of all randomized patients, irrespective of whether and how much of the interventional strategy they received. The primary end point was analyzed by using survival analysis for cumulative event rates including Kaplan-Meier estimates and Cox regression for calculation of adjusted hazard ratios. Proportional hazards assumptions were confirmed to have been met based on plots of log(time) vs log (−log[survival]). The primary analysis was adjusted for 4 predefined strong predictors of the composite primary end point (death or AHF rehospitalization within 180 days): age, AHF hospitalization in the year before inclusion, systolic blood pressure, and serum creatinine level.[24-26] In a post hoc analysis, site effect was assessed by mixed-effects modeling with site as a random effect. Interaction tests were conducted between the treatment group and the subgroup variables using Cox regression models with tests for interaction to evaluate the consistency of treatment effects. Prespecified subgroups are described in the eAppendix in Supplement 2. No adjustments for multiple comparisons were made; therefore, findings for analyses of secondary end points should be interpreted as exploratory. All hypothesis testing was 2-sided and $P<.05$ was regarded as statistically significant. SPSS version 25.0 (IBM) and R version 3.5.1 (R Foundation) statistical software were used.

Figure 1. Flow of Participants Through the GALACTIC Trial



[a] The number of patients assessed for eligibility is not reported because it was not collected at all sites.

[b] No further follow-up data were obtained. All information up to withdrawal of consent was used in analysis.

Results

Study Population

From December 10, 2007, to February 19, 2018, patients were enrolled in 10 centers in 5 countries. Patients were randomized a median of 5.0 hours (interquartile range, 3.4-7.6 hours) after presentation to the emergency department. Of the 788 patients randomized (**Figure 1**), 781 (99.1%) were eligible for the analysis of the primary end point. The groups were well balanced with respect to baseline characteristics (**Table 1**). Median age was 78 years, 37% were women, 59% had chronic HF, median LVEF was 36%, and coronary and hypertensive heart disease were the most common underlying cardiac disorders. Median time from onset of dyspnea to emergency department presentation was 6 days. The last follow-up was completed in February 2019, and complete clinical follow-up at 180 days was available in 779 patients (99.7%).

Primary End Point

Among 781 patients eligible for the analysis of the primary end point, all-cause death or adjudicated AHF rehospitalization through day 180 occurred in 117 patients (30.6%) in the early intensive and sustained vasodilation group and in 111 patients (27.8%) in the usual care group (absolute difference, 2.8% [95% CI, −3.7% to 9.3%]; adjusted hazard ratio, 1.07 [95% CI, 0.83-1.39]; $P = .59$) (**Figure 2**). This was confirmed in a post hoc analysis using mixed-effects modeling with site as a random effect (adjusted hazard ratio, 1.07; 95% CI, 0.83-1.39; $P = .61$) (eTable 4 in Supplement 2).

Predefined subgroup analyses showed consistent results in 7 of 8 subgroups including those defined by age and LVEF, while indicating a statistically significant interaction of the treatment effect according to sex (adjusted hazard ratio [female sex], 1.67; 95% CI, 1.08-2.59; $P = .02$ for interaction) (**Figure 3**).

Key Secondary End Points

There was no significant difference in key secondary end points, including all-cause deaths through day 180 (55 [14.4%] with the intervention vs 61 [15.3%] with usual care; absolute difference, 0.9%; 95% CI, −4.3% to 6.1%) and median length of stay (9 days in both groups; absolute difference, 0 days; 95% CI, −1 to +1 day). Systolic and diastolic blood pressure initially decreased more rapidly in the early intensive and sustained vasodilation group, eg, to a systolic blood pressure on day 2 of 115 mm Hg vs 125 mm Hg in the usual care group (absolute difference, 10 mm Hg; 95% CI, 6-14 mm Hg; $P < .001$) (**Figure 4**A and eTable 5 in Supplement 2). There was no significant difference between blood pressure measurements on day 1 and after day 3. Improvement of dyspnea, as assessed at levels of 60° and 20° on day 2 and day 6, and reduction of NT-proBNP concentration were not significantly different between groups (eFigure 2 and eTables 6 and 7 in Supplement 2).

Table 1. Baseline Clinical Characteristics and Medical History[a]

Characteristics	Intervention (n = 382)	Usual Care (n = 399)
Age, median (IQR), y	78.0 (70.0-85.0)	77.0 (69.0-84.0)
Sex		
Female	140 (37)	148 (37)
Male	242 (63)	251 (63)
BMI, median (IQR)	26.5 (23.4-30.3)	26.6 (23.5-29.7)
BNP, median (IQR), ng/L	1249 (849-2254) [n = 167]	1272 (845-2146) [n = 220]
NT-proBNP, median (IQR), ng/L	6135 (3359-9899) [n = 167]	5336 (3021-9517) [n = 179]
LVEF, median (IQR), %[b]	36 (26-50) [n = 334]	37 (26-51) [n = 352]
<40	175 (52)	191 (54)
40-49	63 (19)	59 (17)
≥50	96 (29)	102 (29)
Cardiovascular risk factors		
Hypertension	326 (85)	339 (85)
Ever smoked	197 (58)	209 (59)
Dyslipidemia	219 (57)	225 (56)
Diabetes mellitus	122 (32)	139 (35)
Structural heart disease		
Chronic heart failure	231 (60)	229 (57)
Coronary artery disease	220 (58)	233 (58)
Hypertensive heart disease	177 (46)	174 (44)
Percutaneous coronary intervention	105 (27)	107 (27)
Coronary bypass	78 (20)	89 (22)
Myocardial infarction	127 (33)	141 (35)
Valvular replacement	33 (9)	31 (8)
History of atrial fibrillation	192 (50)	200 (50)
Implantable cardioverter-defibrillator	50 (13)	39 (10)
Cardiac resynchronization therapy	27 (7)	22 (6)
Chronic comorbidities		
COPD/asthma	83 (22)	88 (22)
Renal insufficiency	205 (54)	196 (49)
Serum creatinine, median (IQR)		
mg/dL	1.22 (0.96-1.55)	1.19 (0.94-1.58)
μmol/L	108.0 (85.0-136.8)	105.0 (83.5-139.5)
eGFR, median (IQR), mL/min/1.73 m^2[c]	51.5 (37.8-68.8)	52.9 (36.6-72.2)
Peripheral vascular disease	67 (18)	62 (16)
Stroke	64 (17)	66 (17)
Pneumonia	62 (16)	56 (14)
History of pulmonary embolism	26 (7)	16 (4)
Liver disease	28 (7)	29 (7)
Active malignancy	14 (4)	10 (3)
Mental health disorder	44 (12)	57 (14)
Symptoms at or shortly before admission		
NYHA symptom severity class[d]		
III	208 (54)	218 (55)
IV	174 (46)	181 (45)

(continued)

Table 1. Baseline Clinical Characteristics and Medical History[a] (continued)

Characteristics	Intervention (n = 382)	Usual Care (n = 399)
Days with dyspnea, median (IQR)	5.0 (3.0-14.0) [n = 358]	7.0 (3.0-14.0) [n = 380]
Chest pain	93 (24)	105 (26)
Nocturia	211 (55)	242 (61)
Weight gain	189 (49)	193 (48)
Orthopnea	270 (71)	284 (71)
Paroxysmal nocturnal dyspnea	211 (55)	218 (55)
Coughing	180 (47)	199 (50)
Sputum	106 (28)	100 (25)
Fever	14 (4)	18 (5)
Night sweats	49 (13)	58 (15)
Clinical examination		
Heart murmur	145 (38)	157 (39)
Murmur radiation	47 (12)	46 (12)
Third heart sound	27 (7)	30 (8)
Positive hepatojugular reflux	98 (26)	92 (23)
Jugular venous distension	197 (52)	190 (48)
Edema	287 (75)	280 (70)
Ascites	22 (6)	21 (5)
Pulmonary attenuation[e]	87 (23)	66 (17)
Pulmonary wheezing	86 (23)	85 (21)
Pulmonary rales	331 (89)	348 (90)
Vital signs, median (IQR)		
Blood pressure, mm Hg		
Diastolic	75.0 (65.0-86.0) [n = 382]	75.0 (65.0-86.0) [n = 398]
Systolic	130.0 (117.2-145.0)	131.0 (118.0-150.0)
Heart rate, /min	82.0 (70.0-95.0) [n = 380]	81.0 (70.0-96.0) [n = 396]
Respiratory rate, /min	20.0 (18.0-24.0) [n = 339]	20.0 (18.0-24.0) [n = 350]
Oxygen saturation, %	95.5 (93.0-97.0) [n = 374]	96.0 (94.0-98.0) [n = 393]
Temperature, °C	36.5 (36.3-36.8) [n = 119]	36.6 (36.3-36.8) [n = 118]
Triggers of current acute heart failure episode[f]		
Unknown	109 (29)	84 (21)
Arrhythmia[g]	102 (27)	103 (26)
Infection	56 (15)	48 (12)
Uncontrolled hypertension	40 (10)	53 (13)
Volume overload	35 (9)	42 (11)
Nonadherence to medication	25 (7)	46 (12)
Pulmonary disease (pulmonary embolism, COPD)	25 (7)	21 (5)
Medication (NSAIDs, changes in diuretics)	24 (6)	32 (8)
Myocardial ischemia/necrosis	22 (6)	21 (5)
Progressive valvular disease (mitral regurgitation, aortic stenosis)	21 (5)	23 (6)

(continued)

Table 1. Baseline Clinical Characteristics and Medical History[a] (continued)

Characteristics	Intervention (n = 382)	Usual Care (n = 399)
Anemia (<100 g/L)	11 (3)	23 (6)
Alcohol	7 (2)	10 (3)
Dietary indiscretion	4 (1)	5 (1)
Thyroid disorders	5 (1)	2 (1)
Physical, emotional, environmental stress	2 (1)	4 (1)
Myocarditis	0	2 (1)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

[a] Data are presented as absolute No. (%) of participants unless otherwise indicated.

[b] Transthoracic echocardiography was performed using standard techniques and left ventricular ejection fraction (LVEF) was calculated using the biplane method of discs formula.

[c] Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.

[d] New York Heart Association (NYHA) symptom severity functional classes: class I = no limitation during ordinary physical activity; class II = slight limitation during moderate physical activity by dyspnea and/or fatigue; class III = marked limitation of physical activity by symptoms with minimal exertion; class IV = inability to carry out any physical activity without discomfort.

[e] Pulmonary attenuation defined as diminished breath sounds on auscultation as a possible sign of pleural effusion, etc.

[f] Patients could have more than 1 acute heart failure trigger.

[g] Atrial fibrillation, ventricular tachycardia, bradycardia, atrial ventricular block.

Post Hoc Analyses

From days 1 to 5 and 1 to 3, respectively, doses of nitrates and hydralazine were significantly higher in the early intensive and sustained vasodilation group compared with the usual care group, eg, the median dose of nitroglycerin on day 2 was 60 mg in the intervention group vs 0 mg in the usual care group (absolute difference, 60 mg; 95% CI, 50-60 mg; $P < .001$) (Figure 4, B-C). In contrast, on days 3 and 4, doses of furosemide equivalent were lower in the intervention group compared with the usual care group (eg, the median dose on day 4 was 60 mg in the intervention group vs 80 mg in the usual care group; absolute difference, 20 mg; 95% CI, 0-25 mg; $P = .04$) (Figure 4D) and were associated with a slower reduction in body weight (Figure 4F). From day 3 to hospital discharge, up-titration of ACE inhibitors, ARBs, or sacubitril-valsartan was significantly higher in the intervention group compared with the usual care group, with a median absolute increase of 12.5% of target dose (interquartile range, 0%-50%) vs 0% of target dose (interquartile range, 0%-25%) (absolute difference, 12.5%; 95% CI, 0%-25%; $P < .001$) (Figure 4E). Other concomitant medications used during the study in both groups are presented in eTables 8 and 9 in Supplement 2.

At 180 days, 22% of patients in the early intensive and sustained vasodilation group vs 16% in the usual care group attained the target dose of the prescribed ACE inhibitor, ARB, or sacubitril-valsartan (absolute difference, 6%; 95% CI, 0.3%-11.6%; $P = .04$). The percentage of patients receiving the medications and the prescribed percentage of the target dose at presentation, discharge, and 180 days are presented in eTables 10 and 11 in Supplement 2.

Adverse Events

The most common clinically significant adverse events following early intensive and sustained vasodilation vs usual care, respectively, were hypokalemia (23% vs 25%), worsening renal function (21% vs 20%), headache (26% vs 10%), dizziness (15% vs 10%), prolongation of index hospitalization (10% vs 6%), and hypotension (8% vs 2%) (**Table 2**).

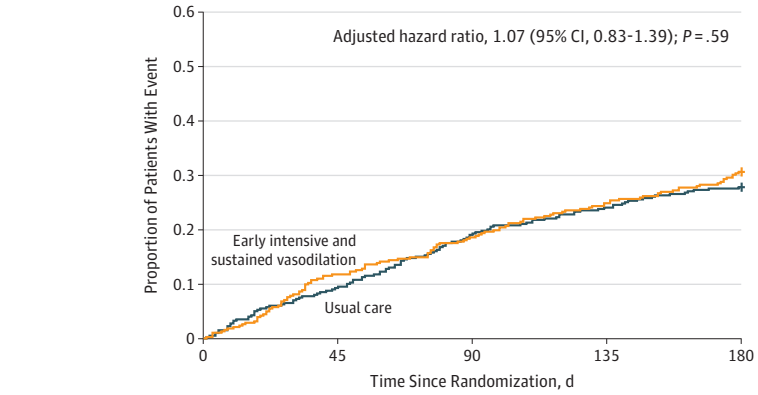
Discussion

In this randomized clinical trial that included 788 patients hospitalized for AHF, a strategy that emphasized early intensive and sustained vasodilation, compared with usual care, resulted in no significant difference in the primary end point of 180-day all-cause mortality and AHF rehospitalizations. This trial has several unique features: it tested a comprehensive strategy of early intensive and sustained vasodilation using individualized doses of well-characterized, widely available, and mostly inexpensive drugs, rather than a single novel and usually expensive drug at a fixed dose.

This study extends and corroborates findings from previous work on the treatment of patients with AHF, particularly 3 large phase 3 trials of novel vasodilators (neseritide, ularitide, and serelaxin) and a moderate-size (n = 308) investigator-initiated direct comparison of diuretic strategies, all 4 of which also provided neutral findings.[5,7,29] Overall, these trials suggest that short-term interventions such as vasodilation may not influence long-term outcomes in the heterogeneous AHF population, even when applying individualized and aggressive dosing strategies as in this trial.[5,7,29] Median time from emergency department presentation to randomization was 5 hours in this study, which was even shorter than that achieved in the other 4 trials.[5,7,29] Patients enrolled in this study were representative of the broad AHF population presenting to emergency departments in North America and Europe.[6,30] Median LVEF in this study was 37% compared with a mean of 39% in a US registry and a mean of 39% in the phase 3 study of serelaxin.[6,30]

From a broader perspective, these trials also suggested that pulmonary congestion, although the hallmark of AHF, may not be the ideal target for novel therapies. Part of the rationale for a possible beneficial long-term effect of vasodilators in AHF was to ameliorate pulmonary congestion without the established detrimental effects of loop diuretics.[5,7,29] Recently, this rationale has been challenged by 2 lines of evidence: first, long-term studies documenting that the beneficial effect of hemoconcentration (ie, effective decongestion) seems to offset worsening renal function,[31,32] and second, a randomized trial showing that the use of a stepped diuretic therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function.[33] In agreement with these recent observations, this trial showed that early intensive and sustained vasodilation did not lead to more rapid improvement in dyspnea or more rapid reduction in NT-proBNP concentrations compared with usual care with its use of higher doses of loop diuretics. Therefore, among AHF patients after initial stabilization in the emergency department, relative to

Figure 2. Kaplan-Meier Estimates of the Primary End Point of Cumulative All-Cause Mortality or Acute Heart Failure Rehospitalization Within 180 Days Among Patients Treated With Early Intensive and Sustained Vasodilation vs Usual Care

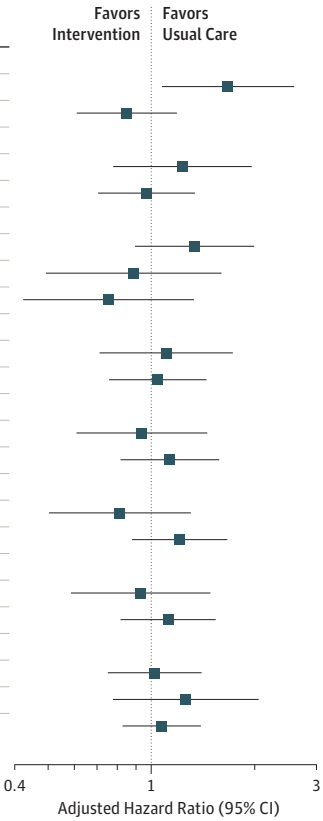


No. at risk					
Early intensive and sustained vasodilation	382	337	311	287	265
Usual care	399	361	322	303	288

Median observation time, 180 days (interquartile range, 136-180 days) in the early intensive and sustained vasodilation group vs 180 days (interquartile range, 141-180 days) in the usual care group.

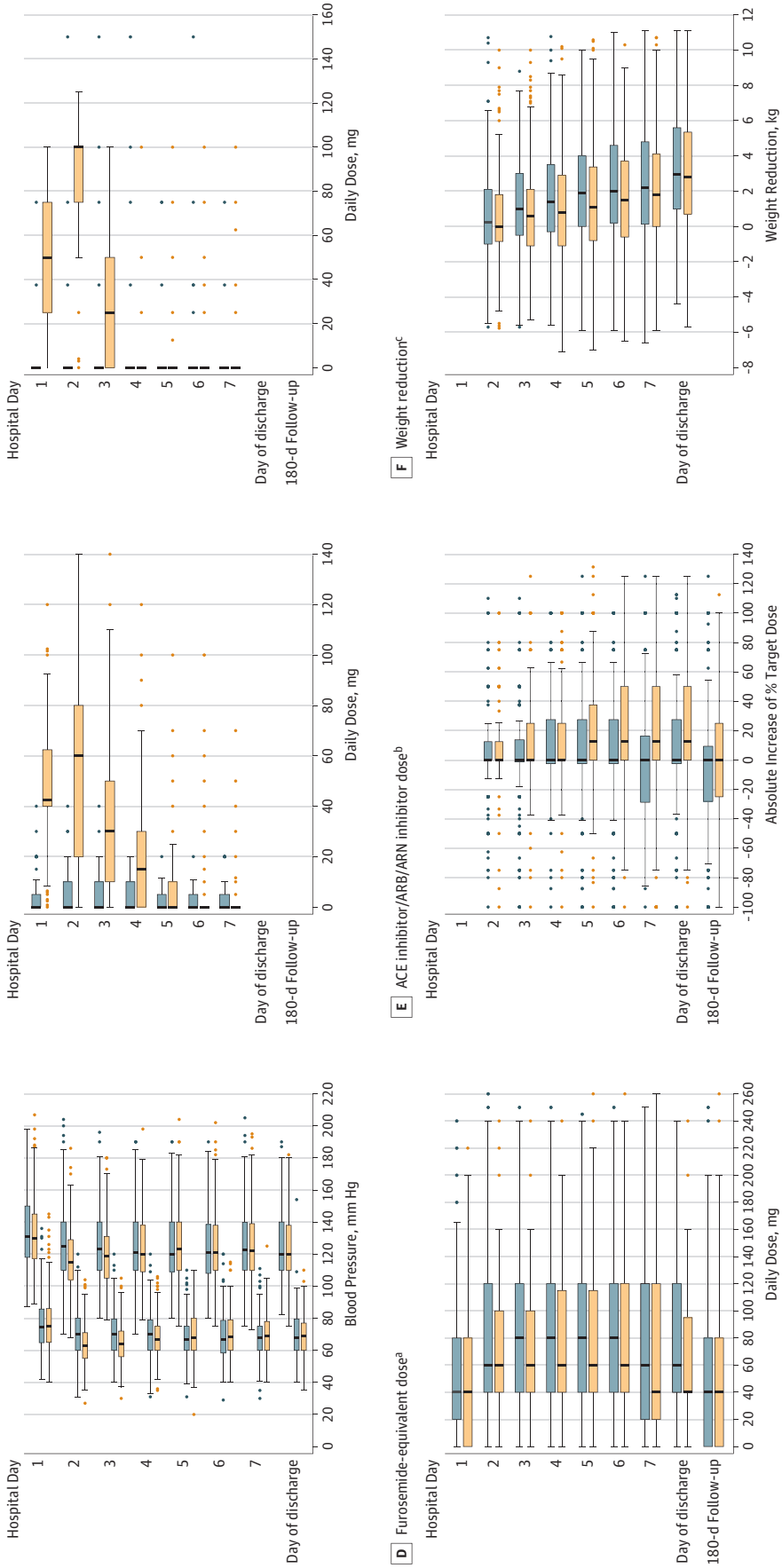
Figure 3. Risk of All-Cause Death or Acute Heart Failure Rehospitalization Within 180 Days in Prespecified Subgroups Among Patients Treated With Early Intensive and Sustained Vasodilation vs Usual Care

Prespecified Subgroups	No. of Primary Composite End-Point Events/Total No.		Adjusted Hazard Ratio (95% CI)	*P* Value	*P* Value for Interaction
	Early Intensive and Sustained Vasodilation (n = 382)	Usual Care (n = 399)			
Sex					
Female	53/140	34/148	1.67 (1.08-2.59)	.02	.02
Male	64/242	77/251	0.85 (0.61-1.19)	.35	
Age, y					
<75	43/144	34/159	1.23 (0.78-1.95)		.29
≥75	74/238	77/240	0.97 (0.70-1.34)		
LVEF, %					
<40	56/175	44/191	1.34 (0.90-1.99)		
40-49	23/63	23/59	0.89 (0.50-1.60)		.21
≥50	22/96	29/102	0.76 (0.43-1.33)		
Systolic blood pressure at randomization, mm Hg					
<120	43/107	37/103	1.11 (0.71-1.72)		.72
≥120	74/275	74/296	1.05 (0.76-1.45)		
Known coronary artery disease					
No	41/162	43/166	0.94 (0.61-1.45)		.57
Yes	76/220	68/233	1.13 (0.82-1.57)		
History of heart failure					
No	31/151	41/170	0.81 (0.51-1.30)		.17
Yes	86/231	70/229	1.21 (0.88-1.66)		
BNP concentration at randomization, ng/L					
<1000	36/145	37/158	0.93 (0.59-1.48)		.61
≥1000	81/237	74/241	1.12 (0.82-1.54)		
eGFR at randomization, mL/min/1.73 m^2					
<60	82/248	79/244	1.03 (0.75-1.40)		.47
≥60	35/134	32/155	1.26 (0.78-2.04)		
Total	117/382	111/399	1.07 (0.83-1.39)	.59	



BNP indicates B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction. Data on LVEF were not available for 47 of 399 patients in the usual care group and 48 of 382 patients in the intervention group. BNP measurements were not available for 179 of 399 patients in the usual care group and 215 of 382 patients in the intervention group. In those patients, the biological equivalent concentration of BNP was estimated as their N-terminal pro-BNP concentration × 0.2.

Figure 4. Post Hoc Analysis of Medication Doses and Weight Reduction and Prespecified Exploratory Analysis of Blood Pressure in Early Intensive and Sustained Vasodilation vs Usual Care Groups



ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARN, angiotensin receptor–neprilysin. Yellow boxes indicate early intensive and sustained vasodilation; blue boxes, usual care. Bars indicate medians; box bottoms and tops, 25th and 75th percentiles; whiskers, upper and lower adjacent values; dots, outliers. Upper adjacent value is defined as the largest observation less than or equal to third quartile + 1.5 × interquartile range (IQR). Lower adjacent value is the smallest observation equal to first quartile − 1.5 × IQR. Significant differences ($P < .05$) were found between groups for nitroglycerin doses throughout hospitalization, for hydralazine doses from day 1 to day 3, for furosemide-equivalent doses on day 4, for ACE inhibitor, ARB, and ARN inhibitor doses from day 3 to day of discharge, for systolic and diastolic blood pressure on day 2 and day 3, and for weight reduction from day 2 to day 7.

[a] Furosemide-equivalent dose on day 1 corresponds to intravenous furosemide application and on day 2 through 180-day follow-up corresponds to prescribed furosemide and/or torasemide dose × 4.

[b] Absolute increases of percentage target dose of ACE inhibitors, ARBs, and ARN inhibitors are reported starting on day 2. Absolute decreases of percentage target dose are expressed as a negative number (eg, a decrease of ramipril dose from 5 mg/d to 2.5 mg/d corresponds to −25% absolute increase of percentage target dose of ramipril at 10 mg/d).

[c] Weight reduction is reported starting on day 2. In most patients, weight on day 1 was a self-reported estimate and not a measurement.

Table 2. Adverse Events

Adverse Events	No. (%) With Event	
	Intervention (n = 382)	Usual Care (n = 399)
Hypokalemia <3.5 mmol/L	88 (23)	98 (25)
Worsening renal function[a]	81 (21)	80 (20)
Headache	101 (26)	38 (10)
Dizziness	58 (15)	39 (10)
Hyperkalemia >5 mmol/L	41 (11)	28 (7)
Systolic arterial hypotension[b]	29 (8)	9 (2)
Fall	14 (4)	7 (2)
Acute coronary syndrome	5 (1)	1 (<1)
Arrhythmia requiring therapy	2 (1)	3 (1)
Serious adverse events		
All-cause rehospitalization	167 (44)	167 (42)
Rehospitalization for acute heart failure[c]	77 (20)	70 (18)
All-cause deaths	55 (14)	61 (15)
Prolongation of index hospitalization	39 (10)	23 (6)
Transfer to intensive care unit	14 (4)	16 (4)
Cardiopulmonary resuscitation	5 (1)	4 (1)

[a] Worsening renal function was defined as an increase in creatinine to more than 30% of baseline.

[b] Systolic arterial hypotension was defined as systolic arterial pressure less than 80 mm Hg over 30 minutes regardless of presence or absence of symptoms.

[c] Rehospitalization for acute heart failure defined as an unplanned admission to a hospital with a length of stay of at least 24 hours because of symptoms attributed to worsening of heart failure.[2,27,28]

intravenous loop diuretics, the role of acute vasodilation seems to be smaller than previously thought.[1,2] The lower doses of loop diuretics used in the early intensive and sustained vasodilation group may have led to the neutral results regarding improvement in dyspnea and reduction of NT-proBNP concentrations. They may have also at least in part contributed to the neutral effect on death or AHF rehospitalization at 180 days.

Predefined, exploratory, hypothesis-generating subgroup analysis found a statistically significant interaction of the treatment effect regarding the primary end point of all-cause death or AHF rehospitalization with 1 of the 8 subgroups: sex, which suggests possible harm in women. This finding cannot be appropriately explained by the older age or the higher percentage of patients with preserved LVEF among women, as there was no interaction with age or LVEF. Possible contributors to the potentially detrimental effects in women may include smaller body size, lower body weight, different body composition, and lower estimated glomerular filtration rate, all of which could contribute to vasodilator overdose.

Early intensive and sustained vasodilation was associated with several adverse events, most notably an increased rate of hypotension (8% vs 2%). Overall, the rate of hypotension was lower than observed with ularitide but higher than observed with serelaxin in 2 recent phase 3 trials.[5,6] Although the length of hospitalization was not significantly different between the 2 groups, adverse events related to the intervention prolonged hospitalization in 10% of patients.

Protocol-guided rapid up-titration of ACE inhibitors, ARBs, or sacubitril-valsartan during the in-hospital period led to higher percentage target doses at hospital discharge. However, the magnitude of the difference and the percentage target dose achieved was lower than expected. Together with insights gained from 2 recent studies of sacubitril-valsartan in the immediate postdischarge period using predefined outpatient up-titration visits, the findings of this study highlight the importance of the immediate postdischarge period for possible improvements in long-term outcomes.[34,35] The rather low percentage of patients in this study attaining the high "target doses" defined for chronic HF with reduced LVEF seem explained by 4 factors: first, the severity of AHF, which prohibited achieving these target doses in many patients despite protocol-defined up-titration in the hospital; second, the inertia of real-life outpatient postdischarge care, in which doses of ACE inhibitors, ARBs, or sacubitril-valsartan are often not up-titrated; third, the progressive nature of HF, as well as its comorbidities, requiring dose reduction due to, for instance, hypotension, worsening renal function, and falls; and fourth, the high prevalence of patients with AHF with preserved LVEF, in whom no target doses of ACE inhibitors, ARBs, or sacubitril-valsartan are defined.[1,2,36]

Limitations

This study has several limitations. First, the results may not apply to patients with severe renal dysfunction or with systolic blood pressure below 100 mm Hg, as they were excluded. Second, enrollment in this investigator-initiated trial was slow, at least in part due to logistic and funding issues. Because treatment of AHF generally remained unchanged during the conduct of the study, findings should still apply to current clinical practice.[1,2,37,38] Third, this study had low statistical power for the analysis of subgroups and tests of interaction. Therefore, these must be interpreted as exploratory and hypothesis generating. Fourth, the open-label design, which was mandated by the aim to test a strategy, not a single drug, may have introduced a bias in the unblinded assessment of dyspnea at day 2 and day 6, but not in the primary end point of all-cause death or AHF rehospitalization or its individual components, as they were assessed by an independent clinical events committee blinded to group assignment. Fifth, most patients had gradual worsening of dyspnea prior to emergency department presentation. Focusing on patients with acute onset of dyspnea might lead to different results.[3,4] Sixth, the event rate observed in the usual care group was lower than assumed in the sample size calculation. Seventh, the intervention group combined the concepts of early initiation of vasodilator therapy and accelerated initiation and up-titration of chronic oral neurohormonal antagonist therapy. A factorial design separating the 2 could have allowed assessment of the effects of both individually.

Conclusions

Among patients with AHF, a strategy of early intensive and sustained vasodilation, compared with usual care, did not significantly improve a composite outcome of all-cause mortality and AHF rehospitalization at 180 days.

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Supervision: Maeder, Oliveira, Mueller, Socrates, Bayés-Genís, Sionis, Gori, Pfister, Kobza, Erne, Mueller.

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